1. INTRODUCTION

1.1 BACKGROUND

The annual incidence of squamous cell carcinoma of the head and neck (SCCHN) is approximately 40,000 cases per year in the US and 60,000 cases per year in Europe. It is estimated that in the US 12,000 patients will die annually from their disease, and that a similar number of deaths may occur in Europe. The key prognostic factor is the stage of disease at presentation. If the patient presents with early disease, as in 25% of new cases, the standard treatment is surgery, radiation, or the combination of both. Long-term disease-free survival is approximately 70%. In this population, patients are more likely to die from a second primary malignancy (field cancerization) than from loco-regional disease recurrence. On the contrary, for patients presenting with advanced disease (75% of new diagnoses), the failure rate following first-line therapy reaches 70% and the pattern of failure is primarily local and regional recurrence.[1]

Regardless of the disease stage at initial presentation, patients having loco-regional recurrence invariably experience substantial tumor-related morbidity. The need for improved treatments to gain control of regional disease and preserve function in this patient population cannot be over-emphasized. To date, surgery, radiation or both are considered the standard treatment for primary SCCHN. In patients who have failed previous radiation and deemed unresectable, chemotherapy is accepted as a standard approach. The main goal of treatment being the palliation of symptoms.

Several chemotherapy regimens have been used in SCCHN with disappointing success. Among single agents, weekly methotrexate has been considered the conventional palliative therapy with partial response rate < 21% (6 to 45%) lasting two to six months.[2,3,4] Cisplatin (CDDP) monotherapy has a slightly better and more predictable response rate of 28% (14 to 41%), although the toxicity is greater and survival is not affected[3,4]. The combination Cisplatin/Fluorouracil (CDDP/5-FU) has become a standard chemotherapy offered to recurrent patients failing previous surgery and irradiation. This regimen has an overall response rate of approximately 32% and a complete response rate between 5 and 15%.[5] However, durable responses remain rare and survival at 1 year is dismal at 20%.

Patients with disease failing CDDP/5-FU have limited options, most of which include significant potential toxicity (taxane chemotherapy or full dose re-irradiation). Patients who have recurred within one year of standard therapy, or those failing or ineligible for salvage therapy (refractory patients) have no therapeutic option.

A treatment that would clearly offer meaningful clinical benefit to patients with refractory SCCHN remains to be established. This indication continues to be an area of active research.

Over the past decade, the investigation into the etiology of human cancer has identified two categories of genetic events leading to cancer:. 1) the loss of a tumor suppressor gene and 2) the activation of a tumor promoter gene. The most prevalent tumor suppressor gene is p53[6]. It encodes a phosphoprotein that binds chromosomal DNA and regulates cell proliferation. In most

instances, when normal p53 function is lost, most often due to mutation or deletion, the cell's ability to undergo apoptosis is impaired. In the absence of physiological apoptosis, cancer can develop[7,8,9,10].

Mutation in or deletion of the p53 gene has been detected in greater than 50% of tumors in patients with SCCHN.[11,12] Pre-clinical studies in cell cultures and animal models have shown that by introducing a normal p53 gene into head and neck cancer cells with gene transfer technologies, the cancer phenotype of cells derived from head and neck cancers can be reverted[13].

1.1.1 RPR/INGN 201 (Ad5CMV-p53)

RPR/INGN 201 is a constructed adenoviral vector containing the normal p53 gene, driven by a CMV promotor. Pre-clinical studies have shown that cell lines derived from SCCHN could be transduced by RPR/INGN 201. In these cell lines, wild type p53 encoded by RPR/INGN 20 1 was expressed and apoptosis occurred. In rodent models, tumorogenesis of SCCHN cells was-reduced when transduction with RPR/INGN 201 took place, regardless of the presence or absence of mutation in the p53 gene. Several studies suggested, however, that cells with mutated p53 were more sensitive to RPR/INGN 201, than those cells with wild type p53[13].

Phase I studies in patients with advanced SCCHN receiving RPR/INGN 201 via intra-tumoral injections on days 1, 3, 5, 8, 10 and 12 every four weeks have shown that related toxicities are minimal. Additionally, the toxicities reported are not those toxicities commonly associated with chemotherapy. Molecular analysis of tumor biopsies from SCCHN patients treated with RPR/INGN 201 have demonstrated expression of the wild type p53 as a result of gene transfer [data on file]. These observations confirm the feasibility of transgene transfer using RPR/INGN 201 in this patient population, as predicted by pre-clinical studies. More importantly, early Phase II data (175 treated patients) confirm both partial and complete responses of lesions in patients with refractory SCCHN (data on file). The preliminary safety profile from these studies coincides with the low toxicity reported in Phase I studies.

In summary, data from previous studies involving significant numbers of patients have demonstrated that RPR/INGN 201, when administered by intra-tumoral injections in patients with recurrent/refractory SCCHN, has anti-tumor activity and is well tolerated. Study patients have also reported clinical benefits including diminished tumor pain, improved tongue and neck mobility, and speech clarity. Further investigation of RPR/INGN 201 in refractory SCCHN is clearly warranted, especially since few effective therapeutic options currently exist.

A detailed discussion of the pre-clinical and clinical data can be found in the Investigator Brochure [13].

1.2 RATIONALE

Greater than 50% of patients with SCCHN express mutant p53 in their tumors. This mutation is not only associated with carcinogenesis and absent physiological apoptosis, but also a decreased probability of chemotherapy response. Preliminary data from ongoing Phase II studies involving.

patients with recurrent SCCHN treated with intra-tumoral RPR/INGN 201, document anti-tumor activity (lesional CR's and PR's) regardless of tumor p53 mutation status. This activity has been observed in refractory (failing platinum/taxane chemotherapy regimens and/or full dose re-irradiation to the same fields) as well as recurrent (chemo-naive) lesions. Additional to evidence of activity, RPR/INGN 201 offers excellent tolerability in the target population.

Phase II studies of single agent RPR/INGN 201 in patients with refractory SCCHN showed that traditional tumor size measurement [e.g. tumor response by WHO or SWOG criteria] were inefficient in reflecting the anti-tumor activity, which included tumor growth control and the resulting clinical benefits. Measurements did not consistently reproduce the actual tumor changes [tumor softening, central excavation, etc. but with limited changes in the outer margins]. Additionally measurements were often inaccurate because of the nature of the tumor, including the previous surgical and irradiation sequelae which commonly render tumor limits imprecise. Overall, both tumor response and stable disease (by traditional measurements) were predictive of a more favorable outcome, i.e. on quality of life, symptoms and function, and/or pain decrease. However, stable disease, as such, is not a fully validated surrogate endpoint for clinical benefit.

Phase II studies also showed a statistically significant survival advantage for patients treated with the highest dose/intense regimen, compared to the least dose/intense regimen [overall patients population, median overall survival 168 days [3-day @ median 6×10^{10} pfu q 4 weeks schedule] versus 197 days [6-day @ median 6×10^{10} pfu q 4 weeks schedule]. The proposed dose intensity in this study will reproduce the highest dose intensity regimen previously studied.

In the previous trials, survival of patients with refractory disease (as defined in this protocol), with tumor size < 7.5 cm and treated with a 6-day q 4 week regimen was 220 days. It is anticipated that the overall survival of patients with refractory SCCHN treated with methotrexate will be 4 months [literature shows 3-5 months for advanced / recurrent disease].

The proposed study in reproducing the survival outcome observed in phase IIa is powered at 98% two-sided test to establish a survival advantage of RPR/INGN 201 single agent versus methotrexate single agent, 7 months versus 4 months. It will have a 90% power to detect a difference of 4.5 versus 7 months.